TREATMENT OF TETANUS.

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Large doses of antitoxin have been rather commonly used in the treatment of tetanus. By reporting four consecutive cases which recovered following the use of large amounts of antitoxin intravenously, it is hoped to emphasize the value of this form of treatment.

The routine procedures adopted follow very closely those used by Woolf[1] in reporting a successful case.

1. Antitoxin is given in dosages of 10,000 to 20,000 units, intravenously, several times daily until all spasm is gone.
2. Morphin hypodermically and chloretone by rectum are given every four to six hours during the stage of reflex hyperexcitability.
3. Liquid nourishment and large amounts of water are given every two hours.

REPORT OF CASES.

Case I.—G. B., male, aged forty-three years. Admitted May 28, 1919.

Complaint. Abdominal pain and cramps.

Present Illness. Three weeks prior to admission he ran a splinter of wood in his finger. One week later he noticed stiffness of his jaw. Stiffness gradually extended to neck, arms, legs and abdomen.

Physical Examination. Temperature, 101.3°; pulse, 120; respiration, 28.

Patient restless and perspiring freely. Jaw muscles spastic and teeth can be separated about three-quarters of an inch. "Risor sardonicus," marked rigidity of neck, arm, leg and abdominal muscles. Tendon reflexes exaggerated. No pathologic reflexes. Marked reflex hyperexcitability.

Treatment. Routine procedure as above. Morphin, gr. $\frac{1}{6}$; chloretone, grs. xx every six hours.

Antitoxin. May 28, 10,000 units intravenously twice; 3000 units intramuscularly.

May 29, 30, 10,000 units intravenously twice.
May 31, 10,000 units intravenously three times.
June 1, 2, 3, 10,000 units intravenously twice.
June 4, 5, 6, 7, 11, 10,000 units intravenously once.
June 14, 15, 25, 10,000 units subcutaneously once.
Total antitoxin, 213,000 units.
June 25, discharged cured.

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[1] Woolf: Jour. Am. Med. Assn., 1919, lxxii, 1266.

Case II.—E. C., male, aged eight years. Admitted October 8, 1919.

Complaint. Stiffness of jaws and convulsions.

Present Illness. About one month prior to admission the child had gone barefoot and had stubbed its toe, leaving a slight abrasion which healed in about a week. Six days before admission he noticed stiffness of jaw, neck and back. On October 7 he had several convulsions.

Treatment. Routine as above.

Antitoxin. October 8, 30,000 units intravenously.
October 9, 10,000 units intravenously three times.
October 10, 10,000 units intravenously twice.
October 11, 10,000; 15,000 units intravenously three times.
October 12, 10,000 units intravenously three times.
October 13, 15,000; 20,000 units intravenously.
October 14, 20,000 units intravenously twice.
October 15, 16, 20,000 units intravenously three times.
October 18, 20,000 units intravenously twice.
October 19, 20, 20,000 units intravenously three times.
October 21, 10,000 units intravenously three times.
October 22, 10,000 units intravenously twice.
October 23, 24, 10,000 units intravenously.
October 25, 10,000 units; 20,000 units intravenously.
October 26, 27, 28, 29, 10,000 units intravenously twice each day.
October 30, 31, November 1, 10,000 units intravenously once each day.
November 1, developed urticaria.
November 27, discharged cured.
Total antitoxin used 755,000 units.

I am indebted to Dr. Blankenhorn for taking charge of this case and also for the use of a syringe outfit by means of which a small needle can be inserted into a vein, and the antitoxin, together with a small amount of saline, injected under pressure.

Case III.—A. B., female, aged eight years. Admitted June 23, 1919.

Complaint. Stiff jaws.

Present Illness. Two weeks prior to admission the patient ran the point of an umbrella into her foot. Three days ago she suddenly became stiff all over and was unable to chew her food. The day before admission she had a convulsion.

Physical Examination. Temperature, 100.2°; pulse, 128; respiration, 26.

General rigidity; marked "risor sardonicus;" hyperactive reflexes; exalted reflex excitability.

Treatment. Routine procedure as above.

Antitoxin. June 23, 25,000 units intravenously.

June 24, 10,000 units intravenously twice.
June 25, 10,000 units; 5000 units intravenously.
June 26, 5000 intravenously; 15,000 units intravenously.
June 27, 10,000 units intravenously.
June 28, 10,000 units intravenously.
June 29, 15,000 units intravenously.
June 30, 15,000 units intravenously.
July 1, 12,000 units intravenously.
July 2, 15,000 units intravenously.
July 4, 5000 units intravenously.
July 6, 5000 units intravenously.
July 8, 5000 units intramuscularly.
July 10, 5000 units intramuscularly.
July 13, 5000 units intramuscularly.
July 16, 5000 units intramuscularly.
July 19, 5000 units intramuscularly.
July 23, 5000 units intramuscularly.
July 31, discharged cured.
Total antitoxin, 189,000 units.

Case IV.—J. N., male, aged ten years. Admitted April 25, 1920.
Complaint. Sore and stiff foot.

Present Illness. Twelve days prior to admission the patient ran a nail into his foot. Nine days later the foot began to feel stiff and sore. On the day of admission his jaw became stiff and he had a convulsion.

Physical Examination. Temperature, 101°; pulse, 120; respiration, 30.

Muscles generally hypertonic, with a tendency toward opisthotonos. Jaws can be separated about one-half inch. Profuse perspiration. Marked "risor sardonicus." Deep and superficial reflexes exaggerated. Reflex hyperexcitability. No pathologic reflexes.

Treatment. Routine as in preceding case.

Antitoxin. April 25, 20,000 and 10,000 units intravenously.
April 26, 15,000 and 5000 units intravenously.
April 27, 15,000 units intravenously.
April 28, 15,000 units intravenously.
April 29, 15,000 and 18,000 units intravenously.
April 30, 20,000 and 20,000 units intravenously.
May 1, 20,000 units intravenously.
May 2, 10,000 units intravenously.
May 18, 5000 units subcutaneously.
May 23, discharged cured.
Total antitoxin, 188,000 units.

Discussion. *Statistics.* While it is the general opinion that antitoxin is of great value in the treatment of tetanus, it is extremely difficult to draw any definite conclusions as to dosage or mode of administration from published statistics. The most comprehensive figures are those for the cases treated in the British Home hospitals during the years 1914–1917. These tables, compiled by Bruce,[2] and Cummings and Gibson,[3] were carefully reviewed by Ransome[4] and Golla,[5] who agree that no reliable conclusions as to the value of antitoxin can be drawn for the following reasons: (1) Prophylactic treatment modifies the disease by lengthening the incubation period which varies inversely with the mortality rate; (2) no attempt was made to standardize the size of dose, the method of administering or the promptness of treatment. For example, some of the cases reported by Bruce were as follows:

	No. of cases.	Mortality rate.
1914–1915	231	57.7
1916	100	31.0

It is impossible to be sure whether the lowered mortality rate was due to more efficient prophylaxis or because more antitoxin was used in the later series. However, clinically, the serum must have made a favorable impression, for in 1917 the British War Office ordered that 50,000 to 100,000 units be injected within the first few days after symptoms appear.

Method of Administration. Sherrington[6] has reported some experiments regarding the relative value of different routes in giving antitoxin. Monkeys were injected with eight times the lethal dose of tetanus toxin intramuscularly, and in forty-two to seventy-eight hours, tetanus antitoxin, 20 units per kilo, was injected with these results:

	Mortality rate, per cent.
1. Subcutaneous	92
2. Intramuscular	88
3. Intravenous	72
4. Intrathecal	44
5. Bulbar intrathecal	48
6. Cerebral subdural	100

These results would tend to show that for a given dose of antitoxin the intrathecal route was the most efficacious. However, at best, the mortality rate was very high and the results throw no light on the effect of the maintenance of a high concentration of antitoxin in the tissues by repeated injections.

Mode of Absorption of Tetanus Toxin. It is well known that tetanus toxin has a marked affinity for nerve tissue while the peripheral motor nerves have been proved to be the pathways by which it is conducted to the central nervous system. However, on experimental evidence there has been a controversy as to whether the toxin is conducted by means of the axis-cylinders or by the neural and perineural lymphatics. From a therapeutic standpoint it matters greatly as to which of these absorption paths is correct, for obviously if tetanus toxin is conducted by the axis-cylinders only antitoxin can be of little value, while if the lymphatics carry it vigorous antitoxin therapy is indicated.

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[2] Lancet, March, 1919, i, 9.

[3] Ibid.

[4] Ibid., December 2, 1917.

[5] Ibid.

[6] Ibid.

The work of Meyer and Ransome[7] seems to show that the conduction is entirely through the axis-cylinders. They showed that if tetanus toxin were injected subcutaneously in an extremity, and after some time the nerve of this extremity were removed and the extract injected into another animal, it would develop tetanus. However, Teale and Embleton[8] proved by reinjection experiments that after the injection of toxin in an extremity, within a short time, it is present in the blood, liver, spleen, etc., and even in the nerve of the opposite extremity, results which would be impossible if the toxin were conducted entirely by the axis-cylinders. In the same research it was demonstrated that blocking the neural and perineural lymph channels by the injection of iodin or colloids delayed the spread of toxin up the nerve. Furthermore, the experiments of Orr and Róus, confirmed by Teale and Embleton, showed that bacteria can travel along the neutral lymphatic sheath, thus inferring that tetanus toxin with its smaller molecule can do the same. Finally, Robertson[9] injected the peripheral nerve paths with Richardson's blue and found the lymphatics of the motor nerves to be much larger than in the sensory, which would help to explain the more ready conduction of tetanus toxin by the motor nerve paths.

Thus the latest evidence seems to point to at least a partial conduction of toxin by the lymphatic route. As a basis for therapy it would be safest to take the position that Robertson assumes, namely, that tetanus toxin appears in the blood stream and other tissues and can be neutralized by antitoxin at any stage in its passage before its final and relatively undissociable union with the ganglion cells. Consequently, the greatest indication for treatment is to maintain as high a concentration as possible of antitoxin in the blood and lymph stream. This can most readily be done by large and frequently repeated injections, intravenously. The small series of cases reported here would confirm somewhat the efficacy and harmlessness of this method of treatment.

Summary. 1. Four cases of tetanus are reported which recovered after receiving large doses of antitoxin intravenously.

2. War statistics of tetanus treatment by antitoxin are difficult to interpret because of the effect of prophylaxis.

3. Experimental evidence shows that tetanus toxin is at least partly conducted by the perineural lymphatics.

4. Theoretically the maintenance of a high concentration of antitoxin in the blood and lymph is indicated in tetanus treatment.

5. Practically, this may be accomplished by large frequent intravenous injections.

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[7] Arch. Exp. Path. u. Pharm., 1903, xlix, 367.

[8] Jour. Path. and Bact., 1919, l, 23.

[9] AM. JOUR. MED. SC., 1916, clii, 31.